

REMARKS

The Office Action dated October 16, 2003 has been received and carefully studied.

A Request for Continued Prosecution is filed herewith.

The Examiner maintains the rejection of claims 13 and 17-19 under 35 U.S.C. §103(a) as being unpatentable over Bussey, U.S. Patent No. 6,011,148. The Examiner states that Bussey teaches a process of ultrafiltration of nucleic acids using differential pressure as a driving force, from a liquid sample by diluting the sample. The Examiner admits that Bussey does not teach fractionation of DNA fragments, but states that the instant application only describes the process of purifying DNA fragments using ultrafiltration with increased recovery by dilution of the sample, even though the application recites the process as "fractionation".

The rejection is respectfully traversed.

Bussey concerns large-scale tangential flow filtration (TFF), and is dealing with plasmids, which are closed circular DNA. Bussey separates unlike species, whereas claims 13 and 17-19 relate to fractionation of linear nucleic acids in a liquid sample consisting essentially of linear nucleic acids, and separate like species (linear nucleic acids from other linear nucleic acids). The plasmids of Bussey are not linear. Moreover, the dilution step of Bussey is to remove contaminants that are not present in any significant amount in the instant sample (as excluded by the "consisting essentially of" language). Applicants therefore respectfully submit that the skilled artisan would not be motivated to modify Bussey to arrive at the instant invention as claimed. Since Bussey's objective in diluting the sample is very

different, one skilled in the art would not be motivated to modify Bussey and arrive at the present invention.

Perhaps most compelling is the fact that Bussey uses TFF, which is not used in laboratory-scale filtration. Even if TFF could be so used, it would fail for the intended purpose of the instant invention, since the salt concentration would change dramatically over the course of the filtration and thereby undermine the basis for the enhanced separation and recovery achieved by the present invention.

The Examiner newly rejects claims 1-8 under 35 U.S.C. §103(a) as being unpatentable over Bussey in view of WO 00/66723 and Geiger '342, and claims 9-12 as being unpatentable over Bussey in view of Simon and Geiger '342. WO 00/66723 is cited for its disclosure of ultrafiltration to dryness of nucleic acid samples with membranes. Geiger '342 is newly cited for its teaching that both single-stranded and double-stranded nucleic acids are commonly believed to be linear polymers. Simon is cited as disclosing monovalent and bivalent cations for removal of contaminants by centrifugal ultrafiltration. The Examiner concludes that it would have been obvious to filter the Bussey sample to dryness, to use the Simon cations in the Bussey process, and that the DNA of Bussey is linear.

The rejections are respectfully traversed.

The aforementioned differences between Bussey and the instant claims as recited above apply to these claims as well. TFF can't run to dryness. There is always some "hold up" or system operating volume that doesn't get filtered. It's in the pump, the filter stack itself, the holding tank and all the plumbing in between. This is an issue with TFF and skilled artisans have been trying to minimize the

holdup volume. (every gram recovered by Genentech, Genzyme and the like is worth about \$10,000.) At commercial scale TFF we discuss liters to 10s of liters of hold up volume as being low. At the lab scale we have 20ml out of 100ml starting liquid as low. But no one can run TFF to dryness. It can't be done.

In addition, the instant claims were previously amended by stating that the liquid sample consists essentially of linear nucleic acids. The Examiner cites the Geiger reference as evidence that Bussey's DNA is linear. However, as pointed out above, Bussey's plasmids are not linear. Moreover, the Examiner does not address the fact that Bussey's sample does not consist essentially of linear nucleic acids; indeed, Bussey is first removing contaminants.

In further support of the patentability of the instant claims, submitted herewith is a Declaration from Dr. Jack Leonard. In the Declaration, Dr. Leonard explains the process described by Bussey would not have accomplished the improved recovery of shorter (polymerase chain reaction) PCR products as described by the instant invention, nor would one skilled in the art be compelled by Bussey to try to improve recovery of short PCR products using his methods, or variations thereon.

Reconsideration and allowance are respectfully requested in view of the foregoing.

Respectfully submitted,


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